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10/038,984	01/04/2002	Yin-Xiong Li	275.0003 0102	9705
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VIVLEMORE, TRACY ANN				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/038,984

**Applicant(s)**

LI ET AL.

**Examiner**

Tracy Vivemore

**Art Unit**

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 14 October 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 75, 76, 78, 79 and 82-98 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 75, 76, 78, 79 and 82-98 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SF/08)  
Paper No(s)/Mail Date 10/14/08
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

### ***Claim Rejections - 35 USC § 112***

Claims 75, 76, 78, 79 and 82-98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of double stranded RNAs of a length greater than 141 base pairs to inhibit GFP, Zf-T, Pax 6.1 and NKx 2-7 in zebrafish embryos, use of double stranded RNAs of a length greater than 201 base pairs to inhibit HirA in chick neural crest explants and use of double stranded RNAs of a length greater than 187 base pairs to inhibit GFP in NIH3T3 cells, does not reasonably provide enablement for use of double stranded RNAs targeted to any other foreign, endogenous or pathogen genes in all types of vertebrate cells. The specification further does not reasonably provide enablement for an *ex vivo* method that includes treatment of an explanted cell with dsRNA followed by implantation into an organism and does not reasonably provide enablement for using this *ex vivo* method to treat a disease or pathogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a

disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

***The nature of the invention and the breadth of the claims***

The claims are directed to methods of *ex vivo* attenuation of gene expression in a vertebrate cell comprising explanting a cell from a vertebrate organism, supplying the cell with double stranded RNA, and implanting the cell into a vertebrate organism. In the embodiments of claims 96-98, the target gene is associated with a disease or pathogen. In other embodiments the target gene is endogenous, foreign, chromosomal or extrachromosomal; the function of the target gene may be unknown. The claims are further directed to a method that identifies a phenotypic change in the treated cell.

***The amount of direction provided by the inventor and the existence of working examples***

The specification teaches at page 2 that the present invention allows for attenuation of gene expression in a cell and teaches that inhibition of gene function is evidenced by a reduction or elimination of the activity associated with the protein encoded by the target gene. The specification further teaches at page 2 that the attenuation of gene expression is specific for the targeted gene. The specification

contemplates a method of treating or preventing disease or infection in a mammal and teaches at page 4 that the methods of the invention can be used to target an endogenous gene or a pathogen gene for medical applications. The specification also states that the method could be used to treat disease or infection, providing general guidance at pages 15-16 of how the RNA would be delivered to the cell and that endogenous or pathogen genes can be targeted, but provides no specific guidance how to overcome the art recognized problems associated with use of transplanted cells.

The working examples of the specification describe the use of dsRNA to inhibit expression of several well characterized genes, including two reporter genes (GFP and Zf-T) in zebrafish embryos. Each of these examples uses long double stranded RNAs: GFP is targeted with dsRNA of 187 base pairs, Zf-T is targeted with dsRNA of 321 base pairs, Pax 6.1 is targeted with dsRNA of 298 base pairs and Nkx 2-7 is targeted with dsRNA of 141 base pairs. Further working examples describe the use of dsRNA of 201 base pairs targeted to HirA in explanted chick neural crest tissue and the use of dsRNA of 187 base pairs targeted to the reporter gene GFP in NIH3T3 cells. None of the working examples describe *ex vivo* treatment of a cell followed by implantation into any organism for any purpose.

The specification teaches that the instant invention provides a method of attenuating gene expression and states that this attenuation is specific for the targeted gene; however those in the art were aware that administration of dsRNA to vertebrate cells results in a non-specific response that leads to general suppression of protein synthesis and cell apoptosis. The working examples of the specification use long

dsRNA that would be expected to produce this response. There is no disclosure in the specification regarding how to overcome the non-specific effects reported in the prior art when double stranded RNAs are added to vertebrate cells.

***The state of the prior art, the level of ordinary skill in the art and the level of predictability in the art***

The level of ordinary skill in the art is high, however there are several aspects of the invention that are unpredictable in view of the disclosure of the instant specification and the knowledge found in the prior art. These aspects include the limited applicability of the results observed in the specification's working examples to the broad scope of the claims, the unpredictability of RNA interference in vertebrate cells and the unpredictability of using transplanted cells comprising dsRNA for the purpose of treating disease.

Most organisms exhibit an immune response (termed the PKR response) that results in non-specific translation arrest and is triggered by even small amounts of double stranded RNA. This response has precluded the use of dsRNA *in vivo* to specifically attenuate gene expression and the unpredictability of specifically attenuating expression of a target gene in vertebrate cells by RNA interference (RNAi) is evident in both pre-filing and post-filing art, particularly with regard to avoidance of this response. This unpredictability extended for at least a year after the filing date.

The specification describes working examples wherein RNA interference is performed in zebrafish embryos, explanted chick neural crest tissue and cultured rodent

Art Unit: 1635

cells. These experiments use dsRNAs ranging in size from 141-298 base pairs to target both reporter genes and endogenous genes and describe that the targeted gene is attenuated specifically.

However, these results are directly contradictory to what the skilled artisan would expect. For example, Oates et al. (Developmental Biology 2000, of record) teaches that dsRNA injected into early zebrafish embryos produced a nonspecific depletion of several endogenous mRNAs and concluded that "RNAi appears unsuited to application in the zebrafish embryo ...." (page 21, left-hand column).

Zhao et al. (Developmental Biology 2001, of record) also report that injection of dsRNA results in degradation of endogenous mRNA and has a nonspecific effect at the posttranscriptional level.

Caplen et al. (Gene 2000, of record) teach that despite the existence of evidence of co-suppression (another term for RNAi), transfection of dsRNA into mouse NIH 3T3 cells transduced with a retrovirus expressing  $\beta$ gal induced no detectable decrease in gene expression (see pages 102-103). Caplen et al. further teach it is possible that gene, cell-type, or developmentally specific effects influence the balance between specific and non-specific responses to dsRNA. Caplen et al. note that these possibilities would need to be taken into account when considering RNAi in mammalian cell systems.

The use of suitable models is critical in order to predictably extrapolate experimental results to other cell types, but the results observed in the examples are not broadly applicable to all vertebrate cells. While RNAi has been observed in other

vertebrate embryo systems, those in the art question the general applicability of these results. Wianny et al. (Nature Cell Biology 2000, of record) reported that dsRNA can be used as a specific inhibitor of gene activity in the mouse oocyte (targeting c-mos) and preimplantation embryo (targeting E-cadherin or a GFP transgene) without causing a general translation arrest. However, the authors indicate (see page 73, under Discussion) that it is possible the early mouse embryo is incapable of the interferon response that would result in general translation arrest and that there may still be difficulties in using RNAi at later stages.

More than a year after the filing date of this application, the field of RNA interference determined that shorter dsRNA molecules of 21-23 nucleotides could avoid the PKR response in vertebrate cells and provide a more predictable inhibitory response. Elbashir et al. (Nature 2001, of record) recognized the importance of avoiding the PKR response, stating at page 494,

"...it is known that dsRNA in the cytoplasm of mammalian cells can trigger profound physiological reactions that lead to the induction of interferon synthesis. In the interferon response, dsRNA > 30 bp binds and activates the protein kinase PKR and 2', 5'- oligoadenylate synthetase (2', 5' -AS)."

Elbashir et al. confirmed this by demonstrating that introduction of long dsRNAs into NIH3T3 cells non-specifically reduced reporter-gene expression (see page 496, first column). In further experiments Elbashir et al. were able to show for the first time that shorter dsRNAs avoided this non-specific response and effectively inhibited gene expression in a manner specific to the target gene.

Although it was well known in the art that RNA of greater than 30 base pairs induces the PKR response the working examples describe experiments using RNAs



that are much longer; having a length of at least 141 base pairs. The specification briefly contemplates at page 12 that the RNA used in the method can be as short as 25 base pairs but aside from the discussion at page 34 the specification provides no discussion of the PKR response, provides no discussion of how to avoid this response and provides no specific guidance regarding length of the RNA that would direct the skilled artisan to the use of shorter dsRNAs as a way to overcome the PKR response.

The examples provided in the specification are not commensurate with the claims, which are directed to RNA interference performed in any vertebrate cells. The examples use long dsRNA, known to those in the art to induce the PKR response. While the working examples appear to avoid this response the art clearly suggests that administering dsRNA to vertebrate systems, either *in vitro* or *in vivo*, to attenuate target genes is not a reproducible or predictable art because one would expect long dsRNAs to non-specifically inhibit gene expression.

Claims 96-98 are additionally directed to treatment of disease by transplanting cells wherein the targeted gene is associated with a disease or with a pathogen such as a virus or bacterium. While the specification contemplates at pages 15-16 that the disclosed methods can be performed *ex vivo* and can be used to treat disease, there is no specific guidance regarding how treatment is to be performed. The specification provides no working examples describing targeting of any disease or pathogen gene and provides no examples wherein a cell treated *ex vivo* is implanted into an organism for the purpose of treating any disease.

Coburn et al. (Journal of Antimicrobial Chemotherapy 2003, of record) point out that the major impediment to using RNA interference as a therapeutic is that gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example page 754, first column, last paragraph). Those of skill in the art of RNA interference are optimistic about the potential of RNA interference as a therapeutic tool, but even with the advances made subsequent to the filing of the instant application, the field recognizes several years after the time of invention that therapeutic methods are not yet effective.

***The quantity of experimentation needed to make the invention based on the content of the disclosure***

At the time of filing, those of skill in the art were well aware of the non-specific PKR response induced by administration of dsRNA to vertebrate cells which leads to a general suppression of protein synthesis and cell apoptosis. Because the results of the experiments described in the working examples are not generally applicable to all vertebrate cells, one of ordinary skill in the art would not have believed the methods disclosed in the instant specification would produce sequence-specific inhibition of gene expression in vertebrate cells because the administered dsRNA would be expected to activate mechanisms including the PKR kinase and inhibit all gene expression. While those in the art have subsequently determined that dsRNAs of shorter length will provide specific inhibition of expression, the specification provides no specific guidance regarding the length of RNA to be used; merely contemplating that RNAs of 25-400

bases are useful. Therefore in order to perform the claimed invention throughout its full scope at the time of filing the skilled artisan would have had to perform trial and error experimentation to discover the length of RNAs that will provide specific attenuation of expression in all vertebrate cells.

Despite the general knowledge of the PKR response, the instant specification provides no specific guidance of how this response is to be overcome. Because the prior art teaches that administration of dsRNA to vertebrate systems is not a reproducible or predictable art in order to practice the instantly claimed invention throughout its entire scope the skilled artisan would have to engage in undue, trial and error experimentation to determine which genes can be attenuated in the exemplified cells and this experimentation would have to be repeated for each type of cell in which the claimed method is to be performed in order to determine which genes can be attenuated using dsRNA without inducing the interferon response.

For targeting of disease or pathogen genes, one of skill in the art would have to further experiment to determine what disease genes can be inhibited by transplanted cells in order to provide a therapeutic effect.

Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broad claims of introducing any dsRNA for any target gene in any vertebrate cell followed by transplantation into an organism because the art of attenuating gene expression by introducing dsRNA into a cell or organism is neither routine nor predictable. Because one of skill in the art could

Art Unit: 1635

not practice the invention commensurate in scope with the claims without undue, trial and error experimentation the claims are not enabled.

***Response to Arguments***

Applicants traverse the rejection by noting that the full immune response referred to in the rejection is not necessary for cells to exhibit a non-specific response to dsRNAs. This response is a cellular rather than specific response and requires only the components of the PKR pathway. Applicants further refer to several references to demonstrate that those of skill in the art recognized that the PKR response can be observed in cells without a full immune response. The examiner acknowledges the clarification of what is required for the PKR response, but notes that these arguments do not overcome the basis of the rejection, which is that in view of the generally recognized non-specific response to dsRNA, the working examples of the specification cannot be extrapolated to the full scope of the claims, which is any vertebrate cell. Applicants' citation of the Cordell-Stewart, Oates and Zhao references actually supports the non-enablement of the claims. As applicants themselves note, these reference provide teachings of what the skilled artisan knew at the time of filing. Based on these references and the rest of the prior art, those of skill in the art would not at the time of filing have expected the claimed invention to be operative throughout its full scope because they would expect that administration of dsRNA to a vertebrate cell would result in non-specific expression inhibition.

Applicants argue that teachings of how to avoid the PKR response are not pertinent and do not render the claimed invention unpredictable because the claims do not recite language requiring the absence of a PKR response.

This is not persuasive because the claims explicitly recite that the dsRNA used in the claimed invention specifically attenuates the target gene. Since those of skill in the art were well aware of the non-specific cellular response to dsRNA, the claiming of a specific attenuation implies that the invention is to be distinguished from non-specific attenuation. This would require that the PKR response is avoided. If applicants consider the non-specific PKR response to be embraced by the claimed invention they are requested to clearly state this on the record.

Applicants argue that claims 96-98 are not drawn to treating a disease or pathogen, but to a method of attenuating expression of a target gene in a vertebrate cell, where the target gene can be a gene associated with a disease or pathogen.

This is not persuasive because genes associated with diseases and pathogens include causative genes whose inhibition will treat the disease and genes essential to a pathogen whose inhibition will kill the pathogen. These embodiments thus constitute treatment.

Applicants assert that the citation of Coburn is irrelevant and one could use the guidance in the specification to target genes associated with a disease or pathogen.

This is not persuasive because as noted in the rejection even several years after the filing of the instant application use of RNA interference for therapeutic purposes is not routine.

***Claim Rejections - 35 USC § 102***

Claims 75, 76, 78, 79, 82-91 and 93-98 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire et al. (US 6,506,559, of record).

The claims are directed to methods of *ex vivo* attenuation of gene expression in a vertebrate cell comprising explanting a cell from a vertebrate organism, supplying the cell with double stranded RNA and implanting the cell into a vertebrate organism. Specific embodiments recite that the cell is implanted in the same organism, the RNA is less than 200 bases, the RNA comprises at least 25 nucleotides complementary to the target and the RNA is supplied by expression from a DNA sequence or direct delivery. In other embodiments the target gene is endogenous, foreign, chromosomal or extrachromosomal; the function of the target gene may be unknown or it may be associated with a disease or a pathogen such as a virus, bacterium, fungus or protozoan. The RNA may be comprised of a single, self-complementary strand or two strands that may be annealed in the presence of potassium chloride. The claims are also directed to a method that further comprises identifying a phenotypic change in the treated cell.

Fire et al. disclose a method of inhibiting gene expression using a double stranded RNA. At column 10, lines 12-14 the invention is disclosed as including methods performed in cells *ex vivo* (explant cells) and subsequently implanted into an organism. At column 8 the method is disclosed as being performed in vertebrates. The genes targeted can be an endogenous gene or a transgene, which is a foreign gene, or can be from a pathogen (see column 6, lines 45-49). Fire et al. disclose at column 7,

line 67-column 8 line 6 the limitations on hybridization conditions and length recited in the claims; the dsRNAs used in the disclosed examples were purified without phenol and chloroform. The dsRNA can be formed from 1 or 2 strands (see column 4, lines 41-46). The method of Fire et al. can be used to treat disease and the dsRNAs can be delivered via several different means (see column 9, lines 48-64).

Thus, Fire et al. disclose all the limitations of and anticipate claims 75, 76, 78, 79, 82-91 and 93-98.

### ***Response to Arguments***

Applicants traverse the rejection over Fire et al. by stating that if the instant specification is to be considered enabled only for what is exemplified then Fire et al. must be considered enabling only for what the reference exemplifies: use of *C. elegans*. Applicants request that the arguments previously presented in the appeal brief be reconsidered.

The statement that the level of enablement between Fire et al. and the instant specification was identical was made with regard to the use of dsRNA in vertebrate cells. Since the instant specification demonstrates that some genes can be specifically inhibited with long dsRNAs in certain types of cells, the disclosure of Fire et al. is enabling with regard to these specific genes and vertebrate cells. The examiner was not stating that Fire et al. is enabled only for its exemplified embodiments, but that the instant specification confirms the enablement of Fire et al. with regard to certain genes and cells and regrets any confusion that may have resulted from this misinterpretation.



Applicants' previous arguments were directed to the lack of teaching in Fire et al. of how to avoid the non-specific response to double stranded RNA molecules that results in general translational arrest and induction of interferon synthesis. Applicants' arguments rest on the proposition that because of the PKR response undue trial and error experimentation would be required to practice the claimed invention based on the disclosure of Fire et al.

These previous arguments directly contradict the statement presented in the remarks of 10/14/08 that the instant claims "do not recite language requiring the absence of a PKR response". If applicants believe avoidance of the PKR response is not required by the claims, whether Fire et al. teach how to avoid this response is irrelevant to the rejection.

### ***Claim Rejections - 35 USC § 103***

Claims 75, 76, 78, 79 and 82-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (of record) in view of Ekenberg et al. (of record).

The claims are directed to methods of *ex vivo* attenuation of gene expression in a vertebrate cell as described in the previous 102 rejection. Claim 92 recites that the RNA may be treated with RNase prior to delivery.

Fire et al. teach a method of inhibiting gene expression using double stranded RNA. Fire et al. teach that the method is general and target organisms include vertebrates such as fish. The genes targeted can be endogenous or a transgene, which is a foreign gene, or can be from a pathogen. The dsRNA can be formed from 1 or 2

Art Unit: 1635

strands, the method can be used to treat disease and the dsRNAs can be delivered via several different means. At column 9 Fire et al. teach that the RNA can be purified before administration to a cell. Fire et al. do not teach the use of RNase to purify the double stranded RNA prior to administration.

It was well known in the art at the time of invention that RNases such as RNase A and RNase T specifically degrade single stranded RNA in the presence of double stranded RNA. See, for example, Ekenberg et al., who describe a protocol for RNase protection assays. This assay involves hybridization of an RNA probe and target, followed by removal of remaining single stranded RNA with an RNase specific for single stranded RNA in order to leave only RNA that is part of a double stranded structure.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use RNA purified by treatment with RNase in the method of inhibiting gene expression with double stranded RNAs taught by Fire et al. One of ordinary skill in the art would be motivated to purify the RNA used for inhibition of gene expression because Fire et al. specifically suggest use of purified RNA. One of ordinary skill would have been motivated to use an RNase specific for single stranded RNA for purification and would have had a reasonable expectation of success in doing so because the use of single-strand specific RNases in order to distinguish between single and double stranded RNA in RNase protection assays was well known.

Thus, the invention of claims 75, 76, 78, 79 and 82-98 would have been obvious, as a whole, at the time of invention.

### ***Response to Arguments***

Applicants argue that the examiner's statement that claims 75, 76, 78, 79, 82-91 and 93-98 are obvious because they have been rejected under 102(e) as anticipated by Fire et al. is conclusory and does not support an obviousness rejection over these claims. This is not persuasive because as noted in the last response, anticipation is the epitome of obviousness, therefore the reasons that claims 75, 76, 78, 79, 82-91 and 93-98 are obvious can be found in the rejection over 102(e).

Applicants further request that the previous comments be reconsidered. These arguments are unpersuasive for the reasons set forth in the last office action.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance.

Art Unit: 1635

Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

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